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Role of IL-28B genetic variants in HCV-related liver disease severity in patients with different viral genotypes

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Abstract

Reports of the role of host interleukin 28B (IL-28B) genetic variants in liver disease severity in patients with chronic hepatitis C (CHC) have obtained conflicting results. The impact of IL-28B in Asian patients with different viral genotypes remains elusive.

We try to elucidate the effect of IL-28B genetic variants in a large Asian cohort with different viral genotypes.

The association between the IL-28B rs8099917 genotype and liver fibrosis was investigated in 1288 patients with biopsy-proven CHC.

Patients with hepatitis C virus genotype 1 (HCV-1) infection comprised 59.4% of the population. The remaining 40.6% (518 patients) did not have HCV-1 infection. Of the 1084 patients with the IL-28 genotype, 85.6% (928 patients) had the TT genotype. Univariate analysis revealed that, compared to patients without advanced liver fibrosis, patients with advanced liver fibrosis (Metavir fibrosis score 3–4) had an older age, a lower platelet count, a higher α-fetoprotein level, a higher alanine aminotransferase level, a higher incidence of diabetes, and a higher frequency of rs8099917 non-TT genotype carriage.

Logistic regression analysis revealed that factors significantly associated with advanced liver fibrosis included age (odds ratio [OR]/95% confidence interval [CI]: 1.023/1.009–1.037, $P = .001$), diabetes (OR/CI: 1.736/1.187–2.539, $P = .004$), α-fetoprotein (OR/CI: 1.007/1.002–1.012, $P = .009$), platelet count (OR/CI: 0.991/0.988–0.993, $P < .001$), and carriage of the rs8099917 non-TT genotype (OR/CI: 0.585/0.400–0.856, $P = .006$). When patients were classified by viral genotype, factors that had significant independent associations with advanced liver fibrosis in patients with HCV-1 infection included diabetes (OR/CI: 2.379/1.452–3.896, $P = .001$), α-fetoprotein (OR/CI: 1.023/1.012–1.035, $P < .001$), platelet count (OR/CI: 0.99/0.987–0.994, $P < .001$), and carriage of the rs8099917 non-TT genotype (OR/CI: 0.529/0.328–0.854, $P = .009$). In patients who had advanced liver fibrosis but not HCV-1 infection, factors that had significant independent associations with advanced liver fibrosis included age (OR/CI: 1.039/1.016–1.063, $P = .001$) and platelet count (OR/CI: 0.99/0.986–0.995, $P < .001$); additionally, IL-28B genetic variants were not associated with liver disease severity.

Unfavorable IL-28B genetic variants were associated with advanced liver disease. The genetic effect is limited to patients with HCV-1 infection.

Abbreviations: ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, CHC = chronic hepatitis C, CI = confidence interval, FIB-4 = fibrosis index based on 4 factors, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IL-28B = interleukin 28B, OR = odds ratio, SNP = single-nucleotide polymorphism.

Keywords: CHC, IL-28B, liver fibrosis, SNP

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1. Introduction

An estimated 130 to 170 million people worldwide are currently infected with hepatitis C virus (HCV), and more than 350,000 people die from chronic hepatitis C (CHC)-related end-stage liver disease each year.[1] Notably, 50% to 80% of patients acutely infected with HCV eventually have chronic hepatitis.[2] Notably, 10% to 20% of patients with HCV infection are diagnosed with liver cirrhosis within 20 to 30 years. In patients with liver cirrhosis, the annual incidence of hepatocellular carcinoma (HCC) is 1% to 8%. Factors associated with CHC-related liver fibrosis progression and clinical outcome include age, time because initial HCV infection,[3] hepatitis B virus or human immunodeficiency virus (HIV) coinfection, obesity, hepatic steatosis, alcoholism,[4,5] and nonresponse to antiviral therapy.[6,7] The host genetic predispositions are considered another important determinant of progression and outcome in liver fibrosis.[8–15]

Studies based on genome-wide associated studies have shown that single-nucleotide polymorphisms (SNPs) at or near the interleukin 28B (IL-28B) gene play a role in the management of HCV infection. Emerging evidence indicates that favorable genetic variants of IL-28B may increase the efficacy of interferon-based treatment for HCV genotype-1 (HCV-1).[16–20]

However, the literature is inconsistent regarding the impact of what on liver disease severity in CHC patients.[14,21–26] The discordant results may be attributable to diverse study designs and patient characteristics. Notably, most studies of what have been performed in the West, where the prevalence of HCV-1 infection is high. Although viral genotypes reportedly differ in their distribution of IL-28B genotypes,[27] few studies have investigated associations between IL-28B genetic variants and liver disease severity in patients with different viral genotypes. Therefore, the current study investigated this association in a large cohort of Asian patients who had biopsy-proven infection with HCV-1 or HCV-2.

2. Methods

2.1. Patients

This study analyzed 1288 CHC patients recruited from 1 medical center and 2 regional core hospitals from 2001 to 2011. All patients had been referred for pegylated interferon/ribavirin antiviral therapy, and liver biopsy was performed before treatment. The exclusion criteria were coinfection with HIV, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson disease, α_1-antitrypsin deficiency, and any history of the following: alcohol abuse (≥20 g daily), psychiatric condition, liver transplantation, or HCC. Anti-HCV antibodies were detected using a commercially available third-generation enzyme-linked immunosorbent assay kit (AxSYM 3.0, Abbott Laboratories, Chicago, IL). Serum HCV RNA was detected using real-time polymerase chain reaction (COBAS AMPLICOR Hepatitis C Virus Test, ver. 2.0; Roche, Branchburg, NJ, detection limit: 50 IU/mL). The HCV genotypes were determined using the Okamoto method.[28] The biochemical parameters were measured with a multichannel auto analyzer (Hitachi Inc, Tokyo, Japan). The liver histology was graded and staged according to the scoring system described by Scheuer.[29] To overcome the sampling variability in liver biopsies, associations with genetic variants were evaluated in patients with bridging fibrosis (F3–F4) and not in patients who only had cirrhosis.[15,30] The study was approved by the ethics committees at the participating hospitals and was performed according to the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients gave written informed consent before enrollment.

2.2. IL-28B genotyping and statistical analyses

As in previous works, rs8099917 was selected as the candidate SNP.[31,32] The genotypes of the patients were determined using methods described previously.[33] Frequency was compared between groups by chi-squared test with Yates correction or by Fisher exact test. Group means, presented as mean values standard deviation, were compared using analysis of variance and the Student t test or the Mann–Whitney U test. The serum HCV RNA levels were expressed after logarithmic transformation of original values. Severity of liver fibrosis was indicated by the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) calculated by the following equation: (AST level/upper limit of normal range)/platelet counts (10^9/L) × 100.[34] Fibrosis index based on 4 factors (FIB-4) was calculated as age ([year] × AST [U/L])/((PLT [10(9)/L]) × (ALT [U/L])(1/2)).[35] The frequencies of the rare allele (G) of rs8099917 genotype were too low, and the rare homozygote (GG) and heterozygote (GT) were combined in analyses of SNPs. A stepwise logistic regression analysis was performed to evaluate the independent factors associated with advanced liver fibrosis by analyzing the covariants with P values $< .05$ in the univariate analysis. The area under the curve was compared using receiver operating characteristic analysis to determine the cut-offs for using APRI and FIB-4 level to predict advanced liver fibrosis. The statistical analyses were performed using the SPSS 12.0 statistical package (SPSS, Chicago, IL). All statistical analyses were based on 2-sided hypothesis tests with a significance level of $P < .05$.

3. Results

3.1. Patient profiles

Table 1 shows the basic demographic, virological and clinical features of the 1288 patients. The mean age was 52.2 ± 11.7 years, and males comprised 56.0% of the population. The mean HCV RNA levels were 5.4 ± 1.0 log IU/mL. Patients with

Table 1

Baseline characteristics and clinical features of the patients.

	All patients (N = 1288)
Age, y (mean ± SD)	52.2 ± 11.7
Male gender, n (%)	721 (56.0)
Body weight, kg (mean ± SD)	65.3 ± 11.2
Diabetes, n/N (%)	175/1286 (13.6)
Platelet count, $\times 10^3$ μ/L (mean ± SD)	164.1 ± 61.0
AST, IU/L (mean ± SD)	103.2 ± 61.4
ALT, IU/L (mean ± SD)	152.6 ± 97.1
α-Fetoprotein, ng/mL (mean ± SD)	17.3 ± 49.0
HCV genotype 1, n/N (%)	759/1277 (59.4)
HCV viral loads, log IU/mL (mean ± SD)	5.4 ± 1.0
HBsAg (+), n/N (%)	107/1286 (8.3)
IL-28B rs8099917 genotype	928/1084 (85.6)
APRI	1.9 ± 1.6
FIB-4	3.4 ± 2.9

ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, FIB-4 = fibrosis index based on 4 factors, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, IL-28B = interleukin 28B, SD = standard deviation.

Table 2

Univariate analysis of factors associated with advanced liver fibrosis.

	All patients (N = 1288)	F0–F2 (n = 868)	F3–F4 (n = 420)	P
Age, y (mean ± SD)	52.2 ± 11.7	50.4 ± 11.8	56.1 ± 10.4	<.001
Male gender, n (%)	721 (56.0)	498 (57.4)	223 (53.1)	.15
Body weight, kg (mean ± SD)	65.3 ± 11.2	64.9 ± 11.2	66.1 ± 11.3	.08
Diabetes, n/N (%)	175/1286 (13.6)	93/868 (10.7)	82/418 (19.6)	<.001
Platelet count, $\times 10^3$ μ/L (mean ± SD)	164.1 ± 61.0	177.2 ± 55.8	139.9 ± 63.6	<.001
AST, IU/L (mean ± SD)	103.2 ± 61.4	97.3 ± 60.3	115.5 ± 61.9	<.001
ALT, IU/L (mean ± SD)	152.6 ± 97.1	152.6 ± 97.9	152.5 ± 95.7	.99
α-Fetoprotein, ng/mL (mean ± SD)	17.3 ± 49.0	11.5 ± 30.5	29.4 ± 72.4	<.001
HCV genotype 1, n/N (%)	759/1277 (59.4)	510/863 (59.1)	249/414 (60.1)	.72
HCV viral loads, log IU/mL (mean ± SD)	5.4 ± 1.0	5.4 ± 1.0	5.3 ± 1.0	.31
HBsAg (+), n/N (%)	107/1286 (8.3)	80/868 (9.2)	27/418 (6.5)	.09
IL-28B rs8099917 genotype	928/1084 (85.6)	657/746 (88.1)	271/338 (80.2)	.001
APRI	1.9 ± 1.6	1.6 ± 1.3	2.6 ± 2.0	<.001
FIB-4	3.4 ± 2.9	2.7 ± 2.0	4.9 ± 3.7	<.001

ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, FIB-4 = fibrosis index based on 4 factors, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, IL-28B = interleukin 28B, SD = standard deviation.

advanced fibrosis (F3–F4) comprised 32.6% of the population. Patients with HCV-1 infection comprised 59.4%. The remaining 40.6% (518 patients) had HCV-2 (39.4%), HCV-3 (0.1%), or an unclassified HCV genotype (1.1%). Of the 1084 patients with IL-28 genotype, 928 (85.6%) patients had the rs8099917 TT genotype.

3.2. Factors associated with advanced liver fibrosis

Univariate analysis revealed that patients with advanced liver fibrosis were characterized by advanced age, low platelet count, high α-fetoprotein, high AST level, a high proportion of diabetes, and carriage of the rs8099917 non-TT genotype (Table 2). The proportion of patients with TT genotype was significantly higher in patients with mild liver disease (F0–F2) compared to patients with advanced fibrosis (88.1% vs. 80.2%, respectively; $P = .001$). Logistic regression analysis revealed that factors significantly associated with advanced liver fibrosis included age (odds ratio [OR]/95% confidence interval [CI]: 1.023/1.009–1.037, $P = .001$), diabetes (OR/CI: 1.736/1.187–2.539, $P = .004$), α-fetoprotein (OR/CI: 1.007/1.002–1.012, $P = .009$), platelet count (OR/CI: 0.991/0.988–0.993, $P < .001$), and carriage of the rs8099917 non-TT genotype (OR/CI: 0.585/0.400–0.856, $P = .006$). Table 3 shows that the APRI or/and FIB-4 did not change the effect of IL-28 SNP on liver fibrosis.

3.3. Factors associated with liver fibrosis stratified by viral genotype

The effect of IL-28B SNP on liver fibrosis was further explored in patients with different viral genotypes (Table 4). The HCV-1 patients with advanced liver fibrosis were characterized by advanced age, low platelet count, high α-fetoprotein, high AST level, high incidence of diabetes, and carriage of the rs8099917 non-TT genotype. Factors that had significant independent associations with advanced liver

Table 3

Logistic regression analysis of factors associated with advanced liver fibrosis.

	Model 1: without APRI and FIB-4			Model 2: with APRI			Model 3: with APRI and FIB-4		
Variables	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age									
Per 1 y increase	1.023	1.009–1.037	.001	1.024	1.010–1.038	.001			
Diabetes									
No	1			1			1		
Yes	1.736	1.187–2.539	.004	1.690	1.147–2.491	.008	1.880	1.278–2.766	.001
Platelet count									
Per 10^3 μ/L increase	0.991	0.988–0.993	<.001						
α-Fetoprotein									
Per 1 ng/mL increase	1.007	1.002–1.012	.009	1.005	1.000–1.010	.06	1.005	1.000–1.010	.03
AST									
Per 1 IU/L increase				0.990	0.986–0.994	<.001	0.996	0.993–0.999	.01
IL-28B rs8099917 genotype									
Non-TT	1			1			1		
TT	0.585	0.400–0.856	.006	0.615	0.420–0.901	.01	0.628	0.427–0.925	.02
APRI				1.949	1.605–2.365	<.001			
FIB-4							1.398	1.295–1.509	<.001

APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, CI = confidence interval, FIB-4 = fibrosis index based on 4 factors, IL-28B = interleukin 28B, OR = odds ratio, TT = rs8099917 TT genotype.

Table 4

Univariate analysis of factors associated with advanced liver fibrosis stratified by HCV genotype.

	HCV genotype 1			HCV genotype non-1		
	F0–F2 (n = 510)	F3–F4 (n = 249)	*P*	F0–F2 (n = 353)	F3–F4 (n = 165)	*P*
Age, y (mean ± SD)	49.6 ± 11.9	55.1 ± 11.1	<.001	51.7 ± 11.5	57.4 ± 9.2	<.001
Male gender, n (%)	315 (61.8)	137 (55.0)	.08	180 (51.1)	82 (49.7)	.78
Body weight, kg (mean ± SD)	65.2 ± 11.3	66.1 ± 10.7	.27	64.4 ± 11.1	66.1 ± 12.3	.13
Diabetes, n/N (%)	53/510 (10.4)	51/248 (20.6)	<.001	38/353 (10.8)	29/165 (17.6)	.03
Platelet count, $\times 10^3$ μ/L (mean ± SD)	179.5 ± 55.5	139.8 ± 64.4	<.001	173.5 ± 56.0	140.3 ± 62.9	<.001
AST, IU/L (mean ± SD)	94.5 ± 60.9	114.1 ± 58.5	<.001	101.9 ± 59.6	118.2 ± 66.9	.008
ALT, IU/L (mean ± SD)	146.6 ± 97.8	150.6 ± 90.4	.58	162.0 ± 97.9	155.8 ± 103.2	.52
α-Fetoprotein, ng/mL (mean ± SD)	10.4 ± 24.7	32.7 ± 79.8	<.001	13.2 ± 37.6	24.7 ± 60.2	.03
HCV viral loads, log IU/mL (mean ± SD)	5.6 ± 1.0	5.6 ± 0.9	.69	5.1 ± 1.0	5.0 ± 1.0	.25
HBsAg (+), n/N (%)	56/510 (11.0)	13/248 (5.2)	.01	24/353 (6.8)	12/165 (7.3)	.84
IL-28B rs8099917 genotype						
TT, n/N (%)	398/455 (87.5)	150/199 (75.4)	<.001	254/286 (88.8)	120/137 (87.6)	.71
APRI	1.5 ± 1.2	2.5 ± 1.9	<.001	1.7 ± 1.4	2.7 ± 2.1	<.001
FIB-4	2.6 ± 1.8	4.8 ± 3.7	<.001	2.9 ± 2.3	5.1 ± 3.7	<.001

ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, FIB-4 = fibrosis index based on 4 factors, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, IL-28B = interleukin 28B, SD = standard deviation, TT = rs8099917 TT genotype.

fibrosis in HCV-1 patients included diabetes (OR/CI: 2.379/1.452–3.896, $P = .001$), α-fetoprotein (OR/CI: 1.023/1.012–1.035, $P < .001$), platelet count (OR/CI: 0.990/0.987–0.994, $P < .001$), and carriage of the rs8099917 non-TT genotype (OR/CI: 0.529/0.328–0.854, $P = .009$). In patients with HCV-non-1 infection, those with advanced liver fibrosis were characterized by advanced age, low platelet count, high α-fetoprotein level, high AST levels, and a high incidence of diabetes but were not characterized by carriage of the rs8099917 non-TT genotype.

Factors independently associated with advanced liver fibrosis in patients with HCV-non-1 infection included age (OR/CI: 1.039/1.016–1.063, $P = .001$) and platelet count (OR/CI: 0.990/0.986–0.995, $P < .001$). The IL-28B genotype was not a determinant of liver fibrosis. The results remained consistent when APRI and/or FIB-4 were considered (Table 5).

Next, the effects of APRI and FIB-4 on pathology fibrosis grade were considered. Both APRI and FIB-4 correlated positively with advanced liver fibrosis in both univariate and logistic regression analyses. Compared with APRI, however, FIB-4 had a stronger

Table 5

Logistic regression analysis of factors associated with advanced liver fibrosis in patients with different HCV genotypes.

	Model 1: without APRI and FIB-4 as covariates			Model 2: with APRI as covariate			Model 3: with APRI and FIB-4 as covariates		
Variables	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
HCV genotype 1									
Diabetes									
No	1			1			1		
Yes	2.379	1.452–3.896	.001	2.280	1.378–3.771	.001	2.381	1.443–3.929	.001
Platelet count									
Per 10^3 μ/L increase	0.990	0.987–0.994	<.001						
α-Fetoprotein									
Per 1 ng/mL increase	1.023	1.012–1.035	<.001	1.020	1.009–1.031	<.001	1.018	1.007–1.029	.001
AST									
Per 1 IU/L increase				0.989	0.983–0.995	<.001	0.996	0.992–1.000	.04
IL-28B rs8099917 genotype									
Non-TT	1			1			1		
TT	0.529	0.328–0.854	.009	0.549	0.341–0.886	.014	0.566	0.349–0.919	.02
APRI				2.081	1.604–2.699	<.001			
FIB-4							1.391	1.250–1.548	<.001
HCV genotype non-1									
Age									
Per 1 y increase	1.039	1.016–1.063	.001	1.041	1.017–1.065	.001			
Platelet count									
Per 10^3 μ/L increase	0.990	0.986–0.995	<.001						
AST									
Per 1 IU/L increase				0.990	0.983–0.997	.004			
APRI				1.909	1.444–2.523	<.001			
FIB-4							1.328	1.217–1.448	<.001

APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, CI = confidence interval, FIB-4 = fibrosis index based on 4 factors, HCV = hepatitis C virus, IL-28B = interleukin 28B, OR = odds ratio, TT = rs8099917 TT genotype.

association with advanced liver fibrosis in HCV-infected patients. When HCV patients were grouped by presence or absence of HCV genotype 1, both groups showed that liver disease severity had a stronger association with FIB-4 compared with APRI.

4. Discussion

This study showed that host IL-28B genetic variants were associated with liver disease severity in Asian patients. Carriage of the unfavorable genotype IL-28B was independently associated with advanced liver disease in Taiwan patients with CHC. Notably, the impacts of host genomes on liver fibrosis differed by viral genotype. In addition, IL-28B SNP only affected liver disease severity in patients with HCV-1 infection.

The determinants of liver fibrosis progression in CHC are multifactorial, and host genetic variants play a critical role. Studies of genome-wide associations and studies of candidate genes have investigated whether host genetic variants are associated with HCV-related liver fibrosis. For instance, Estrabaud et al reported that patients with cirrhosis have higher than normal frequencies of the Mmp1 2G homozygote at position-1607 and the MMP9C allele at position-1562 and that patients with mild fibrosis have a higher than normal frequency of the AA homozygote at position-2518.[36] In CHC patients, carriage of the PNPLA3 rs738409 mutant GG genotype is associated not only with hepatic steatosis,[15] but also with liver fibrosis.[15] All vitamin D receptor gene haplotypes (rs1544410 C, rs7975232 A and rs731236 A, RNP7 rs16851720, and MERTK rs4374383) are reportedly associated with fibrosis progression and cirrhosis development.[9,36] Asselah et al used the expression signatures of 11 genes (KRT 19, COL1A1, STMN2, CXCL6, CCR2, TIMP1, IL8, IL1A, ITGA2, CLDN 4, and IL2) to distinguish the severity of fibrosis from mild to moderate.[37]

In CHC, IL-28B genetic variants are by far the most important host genes in terms of determining the nature of the disease or the outcome of interferon-based treatment. However, their association with liver disease severity remains debatable (Supplementary Table 1, http://links.lww.com/MD/C141).[14,21–26] Some studies have reported that IL-28B genetic variants have a protective effect against liver disease[22,23] whereas other studies have reported that IL-28B genetic variants are associated with poor liver-related outcomes.[14,21,24,25]

In Italy, a study of cirrhotic patients found that those who carried the rs12979860-C allele were less likely to develop end-stage liver diseases or undergo liver transplantation.[23] Fabris et al similarly reported that the rs12979860 C-allele has a protective effect against the development of HCC.[23] By contrast, Barreiro et al reported that some IL28B rs12979860 CC carriers with HCV/HIV infection had a good response to interferon-based treatment but progressed to cirrhosis more rapidly.[21] Some studies have similarly suggested that the IL28B rs12979860 CC genotype is associated with hepatic necroinflammation, progression to advanced fibrosis, and worse clinical outcomes.[14,25] The association between favorable IL-28B genotypes and advanced liver disease may be attributable to a strong immune response. That prior no responders with the IL28B CC genotype may have had a worse outcome than no responders with IL28B non-CC genotypes due to a more vigorous immune response that was insufficient to result in viral clearance, but sufficient to cause greater liver cell injury as evidenced by greater hepatic necroinflammation and serum alanine aminotransferase (ALT) levels.[26] As expected, IL28B genotypes were significantly associated with histological inflammatory activity and with the severity of fibrosis in patients with chronic HCV infection. A possible explanation for the high inflammation in patients with elevated IL-28 production is that this molecule induces expression of interferon stimulated genes, including some inflammatory cytokines.[24]

Notably, few studies have compared the role of the IL-28B genotype in patients with different viral genotypes. Unlike former studies performed in western countries where HCV-1 infection is prevalent, the current study analyzed an Asian cohort in which a large proportion had HCV-2 infection. The role of the IL-28B genotype in liver fibrosis was investigated specifically in patients with different viral genotypes. Our studies showed that the IL-28B rs8099917 non-TT allele is an independent risk factor for advanced liver fibrosis, but only in HCV-1 patients. The exact pathophysiological mechanism is unclear. The result was not consistent with some other researches, which may be attributed to ethnicity differences. In addition, the study was restricted to the cross-sectional design, and we failed to prove whether different fibrosis progressions and long-term outcomes exist in patients with different IL-28B and viral genotypes. The distribution of IL-28B differs by viral genotype.[27] In addition to differences in favorable IL-28B genotype distribution in different viral genotypes, the impact of SNPs on long-term outcomes needs further study. In conclusion, unfavorable IL-28B genetic variants are associated with advanced liver disease in Taiwan patients. However, the genetic effect is limited to patients with HCV-1 infection.

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